REMARKS

Favorable reconsideration of the subject application is respectfully requested in view of the above amendments and the following remarks. Claims 58, 60, and 64-74 were pending in the instant application. Applicants hereby cancel claims 60 and 71 without acquiescence to any rejection and without prejudice to prosecution of the encompassed subject matter in a related divisional, continuation, or continuation-in-part application. Claims 58, 64, 70 and 72 are hereby amended to more specifically point out and distinctly claim certain embodiments of the invention. Support for these amendments may be found throughout the specification and the claims as originally filed, for example, at page 47, line 1 through page 49, line 24, and in Examples 6-11. No new matter has been added.

REJECTION UNDER 35 U.S.C. § 112, FIRST PARAGRAPH

Claim 60 stands rejected under 35 U.S.C. § 112, first paragraph, for allegedly containing subject matter that was not described in the specification in such a way as to enable one skilled in the art to make and use the invention. More specifically, the PTO asserts that claim 60 is directed to methods for determining the presence of ANT1, ANT2, and ANT3 polypeptides in a sample and that undue experimentation would be required to practice the invention when the claimed method does not include any steps that would differentiate between these different ANT isoforms.

Applicants traverse these grounds of rejection and respectfully submit that the subject matter encompassed by the instant claim is fully enabled by the specification and does not require differentiation between particular ANT isoforms. As conceded by the PTO (*e.g.*, Action, page 8), one skilled in the art could use the claimed method to detect ANT polypeptides generally. Nevertheless, solely for purposes of advancing the prosecution of the application without acquiescence to the rejection and without prejudice to further prosecution of the encompassed subject matter in a related application, the rejection of claim 60 is rendered moot by cancellation of this claim according to the amendment submitted herewith. Therefore, the rejection under 35 U.S.C. § 112, first paragraph, should be withdrawn.

REJECTION UNDER 35 U.S.C. § 103

Claims 58 and 64-74 stand rejected under 35 U.S.C. § 103(a) as allegedly obvious over Schultheiss et al. (1983 *Clin. Exp. Immunol.* 54:648) in view of Boulay et al. (1983 *Anal. Biochem.* 128:323-330), Fiore et al. (1998 *Biochimie* 80:137), Rosenburg (1996 *Protein Analysis and Purification: Benchtop Techniques*, Birkhauser, Boston, MA, pp. 170-182 and 303-322), and Osman et al. (1993 *J. Immunol. Methods* 161:97-106). More specifically, the PTO asserts that Schultheiss et al. teach a method for determining the presence of an ANT in bovine mitochondria samples, the method comprising contacting samples with radiolabeled carboxyatractyloside. The PTO concedes that Schultheiss et al. fail to teach a fluorescently labeled atractyloside, and also fail to teach methods for detecting a human ANT. The PTO asserts, however, that Boulay et al. teach synthesis of atractyloside derivatives in which the 6' hydroxyl is substituted with fluorescent substituents, and that Fiore et al. suggest the use of fluorescently-labeled atractyloside molecules to detect the amount of ANT within mitochondria to screen for ANT deficiencies.

The PTO further alleges that the skilled artisan would have been motivated to use the method of Schultheiss et al. to determine the presence of, or to purify, human ANT in human samples as suggested by Fiore et al. The PTO asserts that Rosenburg and Osman et al. teach various protein detection systems such as radiolabeling, biotinylating and fluorescence labeling, and that it would have been obvious to a skilled artisan to modify the method of Schultheiss et al. by using fluorescently labeled atractyloside derivatives as suggested in Fiore et al. and specifically taught in Boulay et al. The PTO further alleges that a skilled artisan would have been motivated to use a fluorescent label that has higher sensitivity in methods of detecting the amount of ANT in patients with myopathies.

Applicants traverse these grounds of rejection and respectfully submit that the PTO has failed to establish a *prima facie* case of obviousness. *See In re Mayne*, 104 F.3d 1339, 1341-43 (Fed. Cir. 1997) (PTO has the burden of showing a *prima facie* case of obviousness.). The PTO must show (1) that the references teach or suggest all claim limitations; (2) that the references provide some teaching, suggestion, or motivation to combine or modify the teachings of the prior art to produce the claimed invention; and (3) that the combined teachings of the references indicate that by combining the references, a person having ordinary skill in the art will

achieve the claimed invention with a reasonable expectation of success. When rejection of claims depends upon a combination of prior art references, a teaching, motivation, or suggestion to combine the references must exist. (*See In re Rouffet*, 149 F.3d 1350, 1355 (Fed. Cir. 1998)).

Applicants submit that the cited documents, alone or in combination, fail to teach or suggest each and every limitation of the claimed invention and further fail to provide any teaching, suggestion, or motivation to combine or modify the teachings of one or more of the cited documents, or any other prior art, to produce the claimed invention.

In particular, the prior art fails to contemplate ANT ligands that are atractyloside derivatives having the recited structure according to the amendment submitted herewith, and the PTO fails to establish that *a priori*, a person having ordinary skill in the art would have had any motivation to arrive at the presently claimed methods using the recited atractyloside derivative structure *per se*. More specifically, and with regard to Boulay et al. alone or in combination with any other prior art, for any encompassed embodiments employing the atractyloside derivative structure as recited in presently amended claims 58 or 72, R_1 cannot be hydroxyl, and where R_1 is -OC(=O)R_4, R_4 cannot be -X-aryl or -X-substituted aryl. The amended claims affirmatively recite what R_1 and R_4 may be, and the prior art fails even remotely to contemplate arriving at these particular atractyloside derivative structures for use in the presently claimed methods. The present amendments are not, and should not be construed as, an acquiescence to the instant rejection. Rather, Applicants merely wish to expedite the allowance of certain specific embodiments that are disclosed in the application, and reserve the right to continue prosecution of the canceled subject matter is one or more related applications.

Schultheiss et al. merely describe detection of bovine ANT in a sample using radiolabeled carboxyatractyloside, a known atractyloside derivative that is structurally distinct from, and that fails in any way to suggest, the atractyloside derivative having a structure as recited in independent claims 58 and 72 according to the present amendment. In particular, carboxyatractyloside as provided by Schultheiss et al. is *not* substituted at the 6' hydroxyl position, which *is* a feature of the presently recited atractyloside derivative structures.

Schultheiss et al. also teach detection of human ANT in samples from cirrhosis patients, using antibodies that specifically bind to an ANT polypeptide. In this regard, Applicants submit Schultheiss et al. teach away from the present invention, because the

Schultheiss method for detecting human ANT would change the principle of operation of the method for determining the presence of human ANT by employing antibodies, and not an atractyloside derivative, to detect human ANT. Applicants therefore agree with the PTO that Schultheiss et al. fail to teach detection of a human ANT polypeptide in a sample by detecting binding of the human ANT polypeptide to a fluorescently labeled atractyloside.

Applicants submit that when all publications cited by the PTO are taken together, no motivation can be found to use an atractyloside derivative having the presently recited structure in the methods presently claimed. Thus, Boulay et al. disclose certain fluorescent atractyloside derivatives but these authors fail to teach, suggest or otherwise motivate an ordinarily skilled artisan to arrive with the requisite reasonable expectation of success at the presently recited atractyloside derivative structures, for use in a method for detecting a human ANT polypeptide in, or isolating such a polypeptide from, a biological sample. Fiore et al. also fail to teach or suggest the presently claimed method, instead merely describing the quantification of carboxyatractyloside binding sites in a sample by competition assays with a known fluorescent atractyloside compound that in no way contemplates the structure of the atractyloside derivative having the structure recited in the instant claims *per se*. Furthermore, the method of Fiore et al. relates to detection of the *release,* and not the *binding*, of the fluorescently labeled atractyloside compound described therein. Fiore et al. fail to teach or suggest any desirability of combining the methods disclosed therein with any other methods known to the art, and Schultheiss et al., Boulay et al., and Fiore et al. certainly do not offer any suggestion to modify an ANT ligand with the structural specificity that would be required to arrive at the presently recited atractyloside derivative structures.

Neither Rosenberg et al. nor Osman et al. remedy the deficiencies of the other cited documents. Rosenberg et al. merely describe general methods for labeling ligands for protein detection, and Osman et al. describe use of Eu3+ as a detectable label. Neither reference, however, remotely suggests the claimed method, and neither reference indicates that it would be at all desirable to combine the disclosures therein with any other prior art document to obtain Applicants' invention.

Applicants therefore respectfully submit that the documents cited by the PTO, alone or in any combination, fail to teach or suggest each and every limitation of the claimed

method. Moreover, none of these documents provides the requisite motivation to combine or modify the disclosures therein, in a manner that would permit a person having ordinary skill in the art to achieve Applicants' invention. Accordingly, the claimed invention is nonobvious, as required under 35 U.S.C. § 103, and Applicants respectfully request that this rejection be withdrawn.

NEW REJECTION UNDER 35 U.S.C. § 112, SECOND PARAGRAPH

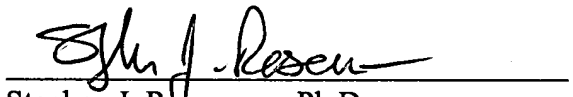
Claim 60 stands rejected under 35 U.S.C. § 112, second paragraph, for indefiniteness. More specifically, the PTO asserts that claim 60 is unclear regarding whether the claim is intended to encompass only one ANT subtype or at least one ANT subtype.

Applicants respectfully submit that in view of the amendments submitted herewith, which include cancellation of claim 60 without acquiescence to the rejection and without prejudice to further prosecution of this subject matter in a related divisional, continuation, or continuation-in-part application, the rejection of this claim is rendered moot.

Applicants respectfully submit that all claims in the application are allowable. Favorable consideration and a Notice of Allowance are earnestly solicited.

Respectfully submitted,

SEED Intellectual Property Law Group PLLC



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